MULTICENTER SEMINARS: IBD (MUSE: IBD)

Going Viral: Management of IBD in the Era of the COVID-19 Pandemic

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Case Presentation

Background

A 40-year-old man with a history of pancolonic ulcerative colitis (UC) since age 27 was diagnosed with COVID-19 (coronavirus disease 2019) disease. He was referred to the Gastroenterology Service in order to determine how to manage his UC therapy.

From age 27–37, his UC disease course was mild. His medication regimen consisted of mesalamine 400 mg twice a day, azathioprine 50 mg daily, and prednisolone 5 mg. He would take these medications intermittently for approximately 1 month at a time when his symptoms flared; otherwise he did not take regular maintenance medications. He returned to medical care at age 37 when he was hospitalized for an unrelated issue. Symptoms at that time consisted of 3–4 bowel movements daily with urgency. Subsequent sigmoidoscopy revealed mild inflammation in the rectum and moderate inflammation (ulceration, erythema, and loss of vascular markings) in the sigmoid, splenic flexure and parts of the proximal transverse colon (Fig. 1). Random biopsies showed cryptitis with increased inflammation in the lamina propria and mild crypt architectural distortion with gland dropout, consistent with his diagnosis.

Based on his symptoms and findings on colonoscopy, the mesalamine dose was increased and changed to a long-acting preparation (Lialda) at 4.8 g daily, and azathioprine was increased to 150 mg daily. A subsequent colonoscopy after 10 months on this regimen showed mucosal healing with a normal-appearing colon without inflammation (Fig. 2). Random biopsies showed focal active colitis in the hepatic flexure and rectum with no inflammation in the cecum, transverse colon, descending colon, and sigmoid colon.

Clinical Course

During a telemedicine visit in gastroenterology, the patient described how he first experienced a fever to 101° Fahrenheit for 2 days, which resolved with acetaminophen and ibuprofen. The fever recurred 10 days later, along with a mild cough. He had no associated shortness of breath, sore throat, diarrhea, abdominal pain, or myalgias. He disclosed that two coworkers had tested positive for infection with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and his wife had also developed a cough. A SARS-CoV-2 test ordered by his primary care doctor was positive, confirming COVID-19. He isolated at home with mild symptoms (cough) and no symptoms suggestive of an IBD flare.

Given the potential for leukopenia with COVID-19, he was instructed to temporarily hold azathioprine but continue Lialda. His case was submitted to an international registry of COVID-19 patients with IBD (Surveillance Epidemiology of Coronavirus Under Research Exclusion, or SECURE-IBD). The decision to restart therapy was left pending based on the resolution of cough and fever for at least 2 weeks and the absence of leukopenia.

Discussion

In December 2019, a cluster of viral pneumonia cases was discovered in Wuhan, China, associated with a seafood and live animal "wet" market. A novel coronavirus (SARS-CoV-2) was identified as the cause and rapidly progressed from an epidemic in China [1–3] to a global pandemic. This virus has caused illness in millions, and as of this writing hundreds of thousands of deaths worldwide. It has disrupted the lives of billions of people through closing of schools,

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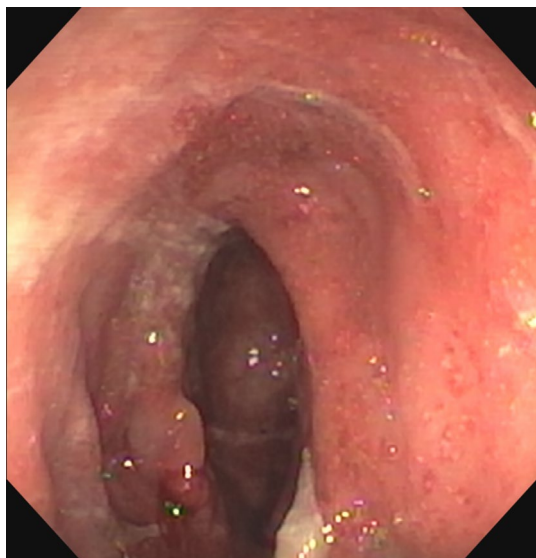
Fig. 1 Colonoscopy demonstrating moderate colitis with ulceration, erythema and loss of vascular markings in the sigmoid, splenic flexure and parts of the proximal transverse colon
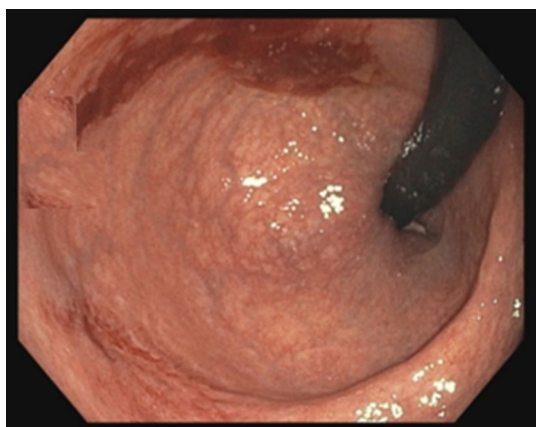

Fig. 2 Most recent endoscopic examinations prior to his COVID diagnosis demonstrating mucosal healing on follow-up colonoscopy 10 months after up-titrating IBD medications

work, and travel. In this setting, this case highlights the following: (1) the increased use of telemedicine during this pandemic for promoting social distancing and avoiding spread of virus in health facilities; (2) how the clinical syndrome caused by the SARS-CoV-2 (COVID-19) may be quite mild and may even go undiagnosed; and finally (3) the dilemma faced by clinicians and patients regarding whether to continue effective immunosuppressive medication in the setting of a contagious infectious pandemic, when the knowledge on the virus and how it affects people with IBD is scarce and evolving. The following report will review key questions relevant for caring for IBD patients during the current pandemic.

What Are the Clinical Manifestations of COVID-19?

An initial case series of 138 patients admitted for COVID-19 in Wuhan reported that the most common presentation was fever, followed by fatigue and dry cough [1]. A larger study of 1099 patients across China confirmed that fever and cough were the most common symptoms [3]. Consistent with these findings, the patient in this case report primarily reported fever and dry cough. About 5–18% also have gastrointestinal symptoms suggestive of viral gastroenteritis with diarrhea, nausea, vomiting, and abdominal pain [3–6]. These GI symptoms are relevant when evaluating an IBD patient with a potential flare. It is important to ask secondary questions regarding fever, cough, and potential exposures through family or coworkers, even though in some cases, GI symptoms are the only clinical manifestations of COVID-19 [7].

Lymphopenia is a common laboratory finding in patients admitted with COVID-19, present in up to 83.2% of cases [3, 8]. Abnormal transaminase and bilirubin levels have been described with severe COVID-19 presentations. These abnormalities are thought to represent the inflammatory response to the virus and collateral hepatic damage due to virally induced cytotoxic T cells [9]. Clinically significant liver injury is uncommon. In our case, the patient did not have any concomitant gastrointestinal symptoms and his ulcerative colitis was under excellent control. Given his mild presentation and outpatient management, no laboratory studies were performed other than his SARS-CoV-2 test.

How Does SARS-CoV-2 Infect the Host?

Knowledge on how the virus enters cells and causes disease is evolving. Though transmission is suspected to occur primarily through respiratory droplets, fecal shedding has also been demonstrated through identification of viral RNA and live virus in stool samples [10]. Toilets have also been contaminated with the virus [11]. Molecular studies suggest that the coronavirus uses the plasma membrane ectoenzyme angiotensin-converting enzyme-2 receptor (ACE2) for cell entry, with binding of the viral spike (S) glycoprotein to cellular receptors via S protein priming by host cell proteases [12]. ACE2 is heavily expressed in the luminal GI tract [13], where it is thought to be involved with amino acid transport (Fig. 3) [14]. A case report has demonstrated the presence of virus presence in gastric, duodenal, and rectal tissue [15].
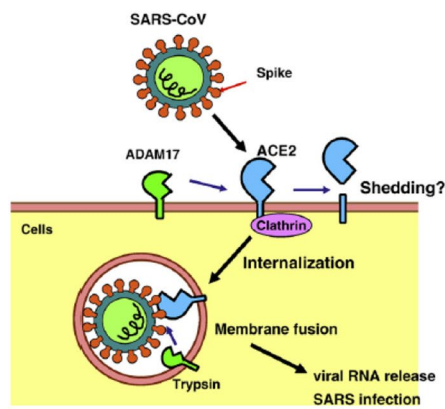
(a) Post-translational modifications of ACE2; internalization and shedding. SARS coronavirus (SARS-CoV) binds to and internalizes with ACE2 for its cellular entry in a Clathrin-dependent manner. Membrane fusion is mediated via activation of Spike by proteases, such as trypsin or furin, and viral RNAs are released into cytoplasm, establishing SARS infection. The transmembrane proteinase (ADAM17) cleaves the extracellular juxtamembrane region of ACE2, releasing the catalytically active ectodomain into the extracellular milieu. Whether such ACE2 cleavage contributes to SARS pathogenesis is not known yet.
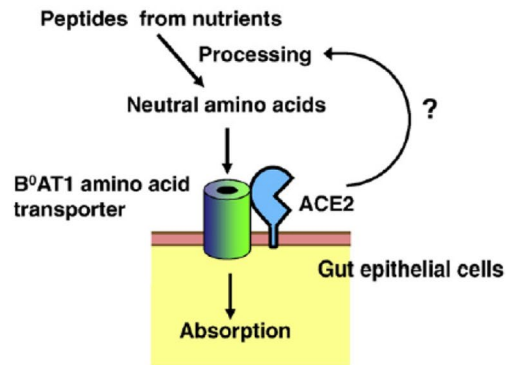
(b) Interaction of ACE2 with the B⁰AT1 amino acid transporter. ACE2 interacts with the B⁰AT1 amino acid transporter ($SLC6A19$) which is required for polarized surface expression of the transporter in gut epithelial cells. Whether ACE2 cleavage contributes to supplying neutral amino acids for the B⁰AT1 is not known yet.

Fig. 3 Illustration of molecular pathway involving ACE2 by which SARS-CoV enters host cells, reproduced from Kuba et al. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther*. 2010. ACE2 is thought to function in amino acid transport. Permission for re-use obtained from Elsevier

Are Patients with IBD at Higher risk of Acquiring COVID-19?

This concern is reasonable, given common IBD medications may affect the host inflammatory and immune responses. Furthermore, the expression of ACE2 may be increased in the inflamed gut of IBD patients, which could theoretically lead to increased entry of the virus into the host [16]. At this time, all available evidence does not suggest IBD patients are at greater risk for acquiring COVID-19 [17]. In a study out of an IBD center in Bergamo, Italy, an epicenter for COVID-19, no patients in a cohort of 522 patients with IBD developed COVID-19 between February 19 and March 23, 2020 [18], close to the pandemic peak in northern Italy. 22% of this cohort was on immunosuppressive therapies including thiopurines, methotrexate, or steroids, and 16% were on a biologic agent (infliximab, adalimumab, vedolizumab, ustekinumab or golimumab). During this same time period, 479 patients without any history of IBD were admitted to the hospital in this region due to COVID-19. At this time, the risk of acquiring COVID-19 is not thought to be any different than the general population. It is not recommended that patients discontinue IBD-related therapy due to the potential risk of developing COVID-19. At this time, there are no guidelines regarding testing of asymptomatic high-risk patients with IBD for SARS-CoV-2. However, some experts believe that for the time being, patients should be tested for SARS-CoV-2 prior to initiating biologic therapy [19].

Could IBD Therapies Be Protective Against Developing ARDS and Severe Disease?

It is postulated that the clinical deterioration and mortality seen in some patients infected with SARS-CoV-2 may be due to an overreaction of the immune system to the virus. This overreaction results in a cytokine release syndrome, characterized by the hyper-activation of T cells and massive production of inflammatory cytokines, including IL-6 [20–22], which can affect the lungs. The result may be acute respiratory distress syndrome (ARDS) and death. While two IL-6 inhibitors (tocilizumab and sarilumab) are undergoing clinical study in COVID-19 patients [23, 24], whether IBD therapies may protect against cytokine release syndrome is as of now, a provocative, but unproven hypothesis [25]. Data from China and Europe regarding the outcomes of IBD patients who do develop COVID-19 are quite limited for answering this question. Whether an international registry (SECURE-IBD [26]) collecting data on IBD patients with confirmed COVID-19 infection may answer this question is to be determined, however, the data are periodically updated and released online at COVIDIBD.org [26].

Are There GI or IBD Society Recommendations on Caring for the IBD Patient During the Pandemic?

Although data are sparse, the American Gastroenterological Association (AGA) recently released a useful paradigm for how to approach the management of IBD during the current COVID-19 pandemic based on the available evidence

Table 1 Recommended management of medications from the International Organization of IBD

Statement	5ASA	BUD	Pred > 20 mg/d	AZA/6 MP	MTX	Anti-TNF	VEDO	UST	TOFA
Medication increases risk of infection with COVID-19	No	No	Yes	?	?	?	No	No	?
Should reduce dose or stop medication to prevent COVID-19 infection	No	No	Yes	No	No	No	No	No	No
Should stop medication if SARS-CoV-2+ but no disease	No	?	Yes	Yes	Yes	?	?	?	Yes
Should stop medication if develop COVID-19 disease	No	?	Yes	Yes	Yes	Yes	?	Yes	Yes

Adapted from IOIBD update [15]

Abbreviations: 5-ASA: 5-aminosalicylate, BUD: budesonide, Pred: prednisone, AZA: azathioprine, 6MP: 6-mercaptopurine, MTX: methotrexate, Anti-TNF: anti-tumor necrosis factor, VEDO: vedolizumab, UST: ustekinumab, TOFA: tofacitinib

and expert opinion [27]. The authors divide the management into three categories based on presentation: IBD patients not infected with SARS-CoV-2, IBD patients infected with SARS-CoV-2 but without manifestations of COVID-19, and lastly IBD patients with confirmed COVID-19 with or without bowel inflammation (our patient). The International Organization of IBD has similarly published a useful guide based on expert opinion, including how to manage various IBD medications (Table 1) [17].

For patients with IBD and not infected with SARS-CoV-2, recommendations are similar to those for the general population: strict social distancing and meticulous hand hygiene. IBD therapies should be continued with a goal of maintaining remission and avoiding flares, steroid use, and hospitalization [24].

For IBD patients infected with SARS-CoV-2 but without manifestations of COVID-19, patients should be switched to lower doses of prednisone (< 20 mg/day) or switched to budesonide if feasible. Thiopurines, methotrexate, and tofacitinib should be temporarily held. Biologic therapies, including anti-TNF agents, ustekinumab and vedolizumab should have their dosing delayed for 2 weeks while monitoring for the development of COVID-19 [27].

For patients currently in remission but with COVID-19, such as our patient, systemic steroids should be avoided and discontinued quickly, if possible. Oral budesonide is likely safe and can continue if needed for controlling disease activity. Thiopurines, methotrexate and tofacitinib should be discontinued during the acute illness. Anti-TNF agents, vedolizumab, and ustekinumab should also be held during the acute illness [27].

Key Points

- The most common presenting symptoms of COVID-19 are fever and dry cough, as was described in this case report. About 5–18% also present with gastrointestinal symptoms suggestive of viral gastroenteritis with diarrhea, nausea, vomiting, and abdominal pain. Lymphope-

nia is a common laboratory finding, and liver enzymes can be mildly elevated in severe cases potentially due to the inflammatory response.

- While SARS-CoV-2 shedding has been demonstrated in stool samples, the primary route of transmission is felt to be respiratory droplets. Additional research is needed to assess the possibility of fecal–oral transmission.

- At this time, available evidence does not suggest that patients with IBD are at increased risk of acquiring COVID-19.

- Patients with IBD who are not infected with SARS-CoV-2 should continue their IBD medications.

- Patients who are infected with SARS-CoV-2 and are asymptomatic, or who develop COVID-19, should temporarily hold any immunosuppressing medications including thiopurines, methotrexate and biologics, and the dose of steroids should be reduced to < 20 mg/day as quickly as possible.

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